Summary of study report - EUPAS 10301

Title

Myozyme (alglucosidase alfa) Safety Information Packet effectiveness evaluation: a healthcare professional survey.

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Main author: Nawab Qizilbash

OXON Epidemiology, C/ Doctor Fleming 51, 28036 Madrid, Spain

Keywords

Additional risk minimisation, Myozyme, safety educational material, HCP survey, assessment of effectiveness.

Rationale and background

During Myozyme procedure EMEA/H/C/000636/II/0052, the European Medicines Agency and the Pharmacovigilance Risk Assessment Committee (PRAC) requested Sanofi Genzyme to further update the existing Myozyme SIP (hereinafter referred to as 'previous SIP') for improvement of readability and content, and to propose a study to evaluate the effectiveness of the new SIP (hereinafter referred to as 'updated SIP'). The survey consists of two waves, wave 1 before the implementation of the updated SIP and wave 2 after the implementation of the updated SIP.

Research questions and objectives

The research questions are:

- Has implementation of the updated Myozyme SIP for the treatment of patients with Pompe disease as an additional risk minimisation measure (RMM) increased: awareness, readability, usage, usefulness, understanding, clinical knowledge and behavioural implementation of key safety messages compared with the previous version of the SIP?
- Has the updated Myozyme SIP been distributed more effectively as compared to the previous version of the SIP?
- What is the opinion of healthcare professionals (HCPs) about the appropriateness of the updated SIP compared to the previous version of the SIP?

<u>Primary objective:</u>
The primary objective is to assess awareness, readability, usage, usefulness, understanding, knowledge of the management of risks associated with Myozyme and behavioural implementation of key safety information contained in the updated SIP as compared to the previous version of the SIP among HCPs.

<u>Secondary objectives:</u>
The secondary objectives are to compare the updated and previous versions of the SIP:

- To assess distribution and format (paper or electronic) of the updated SIP as compared to the previous version of the SIP among HCPs.
- To assess the opinion of HCPs of the appropriateness of the updated SIP as compared to the previous version of the SIP among HCPs.
- To identify major determinants of the degree of awareness, readability, usage, usefulness, understanding, knowledge, utility, utilization and behavioural

implementation of key safety messages contained in the updated SIP among HCPs. Determinants include: type of HCP (physician or nurse), role of the HCP in the management of Myozyme, country, age and gender of the HCP, years in the specialty, number of patients for whom Myozyme was prescribed in the previous 12 months, type of practice, type of institution (academic or non-academic) and participation in Pompe Registry.

Exploratory objective:

- The exploratory objective is to document the reasons for lack of immunological testing with the updated and previous versions of the SIP among HCPs.

Study Design

This is a 2-wave cross-sectional survey to compare the previous and updated versions of the SIP. Wave 1 was carried out before the implementation of the updated SIP and wave 2 after the distribution of the updated SIP in the participating countries.

The start of wave 2 was planned at least 18 months after wave 1 had been completed. However, to ensure the timely submission of the Final Study Report (FSR), this period was reduced to 15 months, still allowing sufficient time for the implementation of the updated SIP in the participating countries.

Setting

The survey was conducted in France, Germany, Italy, Spain, UK and Poland among HCPs (physicians and nurses) who had prescribed Myozyme and/or who monitor patients treated with Myozyme.

The recruitment period for wave 1 extended over a period of 3 months (ie, from mid-April 2015 to mid-July 2015). Data collection was concentrated from mid-June to mid-July, while recruitment was still ongoing. Recruitment in wave 2 started in July and was completed in December 2016. Data collection for wave 2 extended over a period of 1.5 months (ie, from end-Oct 2016 to mid-Dec 2016), after the implementation of the updated SIP in the same participating countries.

Study size

Each wave aimed to recruit approximately 50 prescribers and 50 nurses in the 6 participating countries (France, Germany, Italy, Spain, the UK and Poland).

Variables and data sources

Before the implementation of the HCP survey in each of the participating countries, the questionnaire was cognitively pretested by 1 physician and 3 nurses in the UK and 2 physicians and 2 nurses in each of the participating countries.
The questionnaire comprised of multiple choice and close-ended questions.

Data analyses

Survey participants: The target population includes all HCPs in the participating countries who are involved in the management of Pompe disease patients and have been targeted by the MAH to receive the SIP.

Assessment of representativeness: Representativeness was assessed by performing descriptive analyses on the data collected for each HCP dataset in waves 1 and 2.
Description of the HCP population: All HCP-related variables collected in survey wave 1 are described.

Assessment of the primary endpoints: The primary analysis describes the primary endpoints of awareness, usage, knowledge, understanding, behavioural implementation, readability, and usefulness of the SIP for each wave. Within person and between person comparisons were carried out to assess the effectiveness of the updated SIP.

Assessment of the secondary endpoints: The analysis describes the secondary endpoints of distribution and the opinion of HCPs of the appropriateness of the SIP for each wave. Within person and between person comparisons were carried out to assess the effectiveness of the updated SIP.

Identification of major determinants of primary endpoints: Determinants of primary endpoints were identified through univariate analysis.

Assessment of the exploratory endpoints: The analysis describes the reasons for lack of immunological testing among HCPs for each wave. Within person and between person comparisons were carried out to assess the effectiveness of the updated SIP.

The results are presented in total and stratified by the following factors: country, HCP type, and RM users versus non-users.

Results

Of the target 100 HCPs in each wave, 65 HCPs were deemed eligible and 46 (34 physicians and 12 nurses) were recruited and available for analysis in Wave 1. In Wave 2, 83 HCPs were deemed eligible and 52 (42 physicians and 10 nurses) were available for analysis. The recruitment rate (Full Analysis Set (FAS) / Eligible Set) was 70.8% in wave 1 and 62.6% in wave 2.

Responses were received from the 6 participating countries in both waves. For waves 1 and 2, the corresponding absolute numbers of HCPs (and percentage of each wave) were, respectively: Spain, 12 (26.1%) and 13 (25.0%); Italy, 10 (21.7%) and 9 (17.3%); France, 8 (17.4%) and 12 (23.1%); UK, 7 (15.2%) and 7 (13.5%); Germany, 5 (10.9%) and 6 (11.5%); and Poland, 4 (8.7%) and 5 (9.6%).

HCPs were mainly aged between 46 and 65 years (60.0% in wave 1 and 57.7% in wave 2). At least half of the respondents in each wave were male. Most were physicians (73.9% in wave 1 and 80.8% in wave 2) and 26.1% and 19.2% nurses in waves 1 and 2, respectively. In the UK, only nurses participated in wave 1 and all were female, while in wave 2 two physicians took part. In Poland and Germany no nurse completed the questionnaire. The departments/wards/units of HCPs were mostly neurology/neuromuscular, followed by paediatrics, metabolic units and then endocrine, genetic and other. Most departments were termed academic.

The percentage of HCPs with 1 to 5 years of experience was 37.0% in wave 1 and 28.8% in wave 2. The mean number of Pompe patients managed in the preceding 12 months by HCPs was 4.7 (±5.2) in wave 1 and 6.8 (±9.5) in wave 2. The percentage of HCPs who participated in the Genzyme Global Pompe Registry was 47.8% in wave 1 and 65.4% in wave 2.

Primary endpoints

Awareness. The majority of HCPs were aware and reported having read the SIP. The level of awareness of the SIP was high and improved from wave 1 (75.6%) to wave 2 (82.4%). The within-person pre-post comparison revealed 100% for awareness, as expected. Nurses

fared worse than physicians with awareness: 18.2% versus 94.1%, in wave 1 and 40.0% versus 92.7% in wave 2. The percentage of HCPs who reported having read the SIP was moderately good and similar in waves 1 and 2 (68.9% and 66.7%, respectively). The within-person pre-post comparison revealed similarly good results in wave 1 and 2 (90.5%), with an increase in physicians and a decrease in nurses. Nurses fared worse than physicians with reading: 9.1% versus 88.2% in wave 1, and 10.0% versus 80.5% in wave 2.

Usage. Among those who received or had access to the SIP, 88.2% reported having used it in wave 1 and 91.4% in wave 2. The within-person pre-post comparison revealed for use 95.0% in wave 1 and 90.0% in wave 2.

Knowledge. The overall mean percentage of correct answers to knowledge questions was higher in wave 2 (61.1% ±28.2) than in wave 1 (55.1% ±28.7). Knowledge about immunological, urine and skin testing was also generally higher in wave 2 and statistically significantly higher for the 'false' recommendation of never performing skin testing when an IgE mediated reaction occurs (p=0.049).

Behaviour. The overall mean level of immunological testing was statistically significantly higher in wave 2 (50.3%) than in wave 1 (34.4%) (p=0.024). The within-person pre-post analysis also showed that the mean level of immunological testing improved in wave 2 compared with wave 1 (56.1% versus 48.5%).

There was a reduction from 77.3% in wave 1 to 58.8% in wave 2 in the percentage of HCPs inviting patients to participate in the Pompe Registry at each contact with a Pompe patient. The within-person pre-post analysis showed a reduction of 25.0% in the percentage of HCPs inviting patients to participate in the Pompe Registry every time they saw a patient with Pompe disease.

The overall percentage of HCPs who reported adverse events (AE) with Myozyme increased in wave 2 to 98.0% from 93.2% in wave 1. The within-person pre-post analysis showed no change between wave 1 and 2 in the high percentage of HCPs who reported adverse events with Myozyme.

Readability/understanding. Among HCPs who read the SIP, readability/understanding increased slightly from 80.3% ±13.4 in wave 1 to 83.7% ±13.7 in wave 2. The within-person pre-post analysis showed similar results: 81.2% ±12.1 to 84.0% ±15.2.

Usefulness. The global measure of usefulness of the SIP was considered good and remained stable: 85.1% ±13.9 in wave 1 and 83.9% ±15.6 in wave 2; the within-person pre-post analysis was 85.7% ±15.5 in wave 1 and 89.9% ±10.6 in wave 2.

Global performance. The global performance of the SIP was considered good and remained stable: 72.3% ±16.7 in wave 1 and 73.9% ±15.8 in wave 2; with similar results in the within-person pre-post analysis (72.8% ±18.4 in wave 1 and 77.5% ±15.8 in wave 2).

There were no statistically significant changes in these overall scores of the primary endpoints between the waves with the exception of overall performance of immunological tests (higher in wave 2), though there was a tendency for numerical improvement in most primary endpoints.

Statistically significant differences were only found in awareness and usefulness between the within-person and the independent population in wave 2, to assess the impact of a learning effect on the primary endpoints.

Secondary endpoints

Distribution. Fewer HCPs had received or had access to the SIP in wave 2 (74.5%) than in wave 1 (77.7%), while these figures were reversed in the within-person comparison: 100.0% in wave 2 versus 95.2% in wave 1. Neither of these changes were statistically significant. In both waves, >80.0% received the SIP from the MAH and >65.0% stated the reason as ´unknown´ for not having received or had access to the SIP. Among those who received or had access to the SIP, the percentages who reported having read or referred to the SIP were similar in wave 1 (88.6%) and wave 2 (89.5%).

Appropriateness of the SIP. The vast majority indicated that the SIP was appropriate in both waves; 91.3% in wave 1 and 100.0% in wave 2. Significant differences were detected in the opinion of the usefulness of the SIP for dosing and administration, between the waves: in wave 1, 96.3% HCPs considered the SIP appropriate and 3.7% least appropriate while in wave 2, 81.8% considered the SIP appropriate and 18.2% moderately appropriate. Overall opinion of the appropriateness of readability was also high, with a non-significant decrease in wave 2 to 93.9%, from 96.0% in wave 1.
There were no statistically significant changes in the overall scores of secondary endpoints between the waves, though there was a tendency for slight improvement in many.

The impact of a learning effect on the secondary endpoints was assessed but significant differences were not found except for receipt/access of the SIP and receipt of the SIP after first prescription of Myozyme, with higher levels in wave 2 for the HCPs who had also been involved in wave 1: 76.2% (16/21) and 11.8% (2/17) ($p<0.001$).

Exploratory analyses

The reasons for lack of immunological testing were hindered by much missing data. However, a tendency to increase the performance of all types of testing in wave 2 was observed. In particular, those who reported performing circulating immune complex testing when clinically warranted increased significantly from 28.6% in wave 1 to 54.2% in wave 2 ($p=0.048$). Among HCPs who did not perform these tests, the main reason was that they considered it unnecessary.

Discussion

The overall recruitment rate was low to moderate in both waves and may limit generalisability. However, it should be interpreted in the context of the disease, which is rare, with a limited number of HCPs available for the study.

The pre-post design, allowed within-person and between-person comparisons to be made, which was a strength of the study, the small absolute numbers of HCPs who completed the survey limited the investigation of factors that may influence the overall results.

Although the numbers are small and most changes not statistically significant, there was an overall trend for most measures to improve numerically with the updated SIP. How much of this can be attributed to the updated SIP and how much to the learning and Hawthorne effect in the study design is difficult to unravel due to the small sample size. Improvements numerically in the primary endpoints in both the within-person and between-person comparisons suggest that the learning effect is not the whole explanation. Qualitatively, the updated SIP is a clear improvement on the previous version and this is

supported by extremely high levels of recorded appropriateness, usefulness and readability and understanding, ranging from 90 to 100%. Thus, it would appear that the updated SIP is fit-for-purpose. However, with relatively high levels of appropriateness, usefulness and readability and understanding for the previous SIP, the question arises of whether this risk minimisation measure needed to be improved with an update of the SIP, and if so, was a formal evaluation with an epidemiological study required, rather than with just a qualitative assessment.

With good levels of knowledge and behaviour for the key areas of immunological testing and reporting of ADRs, it would appear that the updated SIP is adequate in performing its function and does not need further improvement.

Marketing Authorization Holder(s)

Genzyme Europe B.V., Gooimeer 10, NL-1411 DD Naarden, The Netherlands.